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EXAMINER
SWITZER, JULIET CAROLINE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/858,200	MAKRIGIORGOS, GERASSIMOS M.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 5-16-03. Claims 1, 2, 4, 5, 6, 9, and10 have been amended. Claims 1-15 are pending, claims 14-15 are withdrawn from prosecution. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 2, 3, 4, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. (US 5459039) in view of Wodicka et al. (Nature Biotechnology, Vol. 15, December 1997).

Modrich et al. teach a method for identifying mutations in a target DNA sequence which comprises

(a) hybridizing the target DNA with a control DNA sequence to create a duplex, wherein the control DNA sequence is the wild-type DNA corresponding to the target DNA sequence (Col. 7, lines 6-8);

(b) tagging any mismatch in said duplex with a detectable moiety, wherein the detectable moiety is a protein (Col. 7, lines 8-10);

(c) cleaving the duplex into segments of 50-300 bases (Col. 13, lines 40-46);

(d) removing the segments tagged with the detectable moiety (Col. 16, lines 15-18), and

(f) identifying the gene and gene segment the selected mismatch belongs to (Col. 16, lines 45-50).

Modrich et al. do not teach a step in which the segments tagged with the detectable moiety are contacted with a mutation scanning array in order to identify the gene to which the segment in the selected mismatch belongs. Thus, the method taught by Modrich et al. differs from the claimed method only in that the methodology used to identify the gene and gene segment to which the selected mismatch belongs is different.

Wodicka et al. provide an array that collectively spans more than 6200 yeast genes, covering all open reading frames with 20 25-mer probes (p. 1359). Wodicka et al. further teach methods in which unknown sequences are hybridized to the arrays and identified based on their location within the array (p. 1366). Wodicka et al. teach a method in which the unknown sequences are amplified prior to hybridization with the array (p. 1366).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used an array such as the one taught by Wodicka et al. for the identification of nucleic acid sequences containing mismatches. The ordinary practitioner would have been motivated by the teachings of Modrich et al. which provide that "any suitable analytical method (Col. 7, lines 40-42)" can be used to identify the fragments and by the teachings of Wodicka et al. who teach that the arrays they provide can be used "for the detection

of genetic differences between strains (p. 1365)." The detection of "genetic differences" is the detection of mutations. Thus, in light of the teachings of Modrich et al. in view of Wodicka et al., the instant invention is prima facie obvious.

4. Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. in view of Wodicka et al. as applied to claims 1-4 and 11 above, and further in view of Beutler (US 5266459).

The teachings of Modrich et al. in view of Wodicka et al. are applied to the instant claim as they were to claims 1-4 and 11. Modrich et al. in view of Wodicka et al. do not teach methods in which non-coding genomic portions of the genes are on the array, nor do they teach arrays that contain genes that are selected because of their association with a disease.

However, the screening of non-genomic portions of genes for mutations or polymorphism was known in the art at the time the invention was made. For example, Beutler teaches a mutation in the second intron glucocerebrosidase gene which is associated with Gaucher disease (ABSTRACT). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have included non-coding regions of genes in an array to be used in a mutation detection method such as the one provided by Modrich et al. in view of Wodicka et al. The ordinary practitioner would have been motivated to utilize arrays containing the coding and non-coding regions of disease genes in the methods taught by Modrich et al. in view of Wodicka et al. in order to have used such arrays in further methods for the detection of disease associated mutations.

5. Claims 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modrich et al. in view of Wodicka et al. as applied to claims 1-4 and 11 above, and further in view of Cronin et al. (WO 98/30883).

The teachings of Modrich et al. in view of Wodicka et al. are applied to the instant claim as they were to claims 1-4 and 11. Modrich et al. in view of Wodicka et al. do not teach methods in which the genes on the array are selected because of their association with particular diseases.

Cronin et al. provide methods for the detection of polymorphisms and mutations in genes (ABSTRACT). The particularly teach that mutations can be searched for in reference sequences that include genes to many different types of diseases and conditions, including cancer, diabetes, and tumor suppressor genes (pages 12-13). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have included any or all of these types of genes on an array to be used in a mutation detection method such as the one provided by Modrich et al. in view of Wodicka et al. The ordinary practitioner would have been motivated to utilize arrays containing the coding and non-coding regions of disease genes in the methods taught by Modrich et al. in view of Wodicka et al. in order to have used such arrays in further methods for the detection of disease associated mutations.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6174680.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Most of the limitations of the rejected claims are recited within the claims of the '680 patent. Limitations that are not specifically recited in the claims are addressed.

The '680 patent claims methods for identifying mutations in a target DNA sequence that comprise the steps (a), (b), (c), (d), (e), (f), (g), (h), (i), and (k) of instant claim 12 (see claim 13 of the '680 patent) and further recites the limitations of instant claim 13 (see claim 14 of the '680 patent). The recitation in at least claim 12 of the '680 patent is encompassed within steps (a)-(e) of instant claim 1. Claim 12 of the '680 patent particularly recites a step wherein the genomic position of the mismatch is determined. The claims of the '680 patent do not particularly recite methods in which the genomic position is determined by applying the mismatch-containing DNA

to a Mutation Scanning Array that comprises a plurality elements that span at least 5 or 10 different genes. The portion of specification of the '680 patent that supports the utilizing the methods claimed in the '680 patent describes an example wherein the genomic positions of the mismatches are determined using an array that has over 6800 genes represented (see example 6 of the '680 patent). Furthermore, the specification particularly discusses arrays that they cal Mutation Scanning Arrays, and discuss the use of these arrays to determine the genomic position of detected mutations (Col. 17-18). They teach that these methods are useful for detecting mutations associated with a wide variety of diseases including cancer and neurodegenerative diseases (Col. 17, lines 35-40). Thus, these limitations in the instant claims cannot be considered patentably distinct over the claims of the '680 patent when there is a specifically recited embodiment of the '680 patent that falls within the scope of the claims herein because it would have been obvious to one having ordinary skill in the art to modify the methods of the '680 patent by selecting a specifically disclosed embodiment that supports that claim, i.e., using the mutation scanning arrays discussed in the specification of the '680 patent. One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within the claims of the '680 patent.

Response to Remarks

Applicant states at page 5 of the response that the invention is specifically directed to using a scanning array to scan at least ten different genes. However, it is first noted that this limitation is not within the claims. The claims require that array itself comprise probes to at least ten different genes, but the active process steps within the claims do not require a step wherein

ten different genes are examined. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., scanning ten different genes) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). However, it is noted that it would be obvious to apply the method disclosed in the cited prior art to detect mutations in a multiplicity of genes, given that it was known in the art at the time the invention was made that mutations occur in many, many different genes in the human genome. It is noted that the addition of such a limitation would require further search and examination by the examiner, to find and consider references which may be relevant to such a limitation.

Applicant argues at page 6 of the remarks that the present invention does not require knowning the identity of the gene containing the mismatch, while Modrich *et al.* begin with genes that are known to them and look for mutations. As before, applicant is arguing a feature that is not present in the claimed invention. The instant claims embrace embodiments wherein the gene being scanned is known or unknown to the practitioner, as the claims do not specify that the gene being scanned is unknown. The teachings of the prior art utilize the method steps of the claimed invention.

With regard to applicant's argument that Modrich does not take advantage of DNA chip technology, this is agreed upon by both applicant and the examiner. This limitation has been provided by the secondary reference. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the

rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that the chip of Wodicka is primarily directed to analysis of gene expression and assessing genetic differences between different strains, citing some examples including detecting chromosomal deletions, duplications, and loss of heterozygosity. Applicant argues that Wodicka in no way teaches a method of detecting a single nucleotide polymorphism. As noted in the rejection, Wodicka specifically teaches that their arrays can be used for purposes other than expression monitoring, especially for the detection of genetic differences between strains (p. 1365 of Wodicka), and they specifically suggest the creation and study of large numbers of mutant strains of yeast for study. Thus, Wodicka the teachings of Wodicka *et al.* in fact do suggest using their arrays to detect mutations, and this encompasses single base pair mutations as well as they types suggested by applicant.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the examiner entirely relies on the knowledge of those of ordinary skill in the art at the time the invention was made, especially citing a teaching from Modrich *et al.* that "any suitable analytical method (Col. 7, lines 40-42)" can be used to identify the fragments and by the teachings of Wodicka et al. who teach that the arrays

they provide can be used "for the detection of genetic differences between strains (p. 1365)." The detection of "genetic differences" is the detection of mutations. Thus, as previously stated, in light of the teachings of Modrich et al. in view of Wodicka et al., the instant invention is prima facie obvious.

Applciant argues the lack of motivation to arrive at the instant invention is apparent given the absence of a suggestion to arrive at the instant invention and the number of DNA chips and bioinformatics applications utilized in the prior art. However, this is not persuasive because, as presented in the rejection and reiterated in the previous arguments, such a suggestion and motivation does exist in the prior art.

Applicant's arguments against the remaining dependent claims rely on the arguments concerning the rejection under Modrich *et al.* in view of Wodicka. These arguments have been addressed, and thus the rejections are all maintained for the reasons of record and those stated herein.

Conclusion

8. No claims are allowed. Claims 12 and 13 are free of the prior art because the prior art does not teach or suggest a method of using a mutation scanning array which includes steps wherein duplexes are treated to remove spontaneous aldehydes, reacted with a repair glycosylase, and then reacted with a compound of the formula X-Y-Z as is recited in step (f) of instant claim 12.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Switzer whose telephone number is 703 306 5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703 308 1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305 3592 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 0196.

Juliet C. Switzer
Art Unit 1634

August 9, 2003

GARY BENZION, PH.D
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